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CORRELATION OF ENDOGENOUS INTOXICATION INDICATORS ON KIDNEY MORPHOLOGY IN SENSITIZED RECIPIENTS AFTER KIDNEY TRANSPLANTATION

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Abstract
This article presents a detailed analysis of the results of examination and treatment of 27 recipients with a high degree of sensitization to the transplant. A study of changes in clinical, laboratory and morphological parameters after transplantation was conducted, with an emphasis on their statistical processing and comparison with data from modern scientific publications. The results of the study indicate a close relationship between endogenous intoxication indicators and morphological changes in the transplant, since the identified morphological disorders in the transplant were found in recipients with elevated levels of endogenous intoxication indicators in the blood.

Keywords: Kidney transplantation, sensitization, treatment of terminal renal failure, endogenous intoxication.

Introduction

According to the World Health Organization, “in the structure of mortality of the population of economically developed countries, kidney diseases rank 7th and account for 2.5–3% of all causes of death” [1,2,14,21,29,30]. Worldwide, about 850 million people have kidney diseases, including chronic kidney disease, acute kidney injury (AKI) and renal failure. According to forecasts, by 2040, CKD will become the fifth leading cause of death in the world. The global prevalence of CKD over this period among all ages increased by 29.3% [2,7,12,19,24,31,32] . Kidney transplantation is considered one of the most effective methods of therapy, which significantly improves the quality of life and increases the survival of patients with end-stage renal disease (ESRD) [9,11,17,22,27,30]. However, for highly sensitized patients, the transplant waiting process may be prolonged or unsuccessful due to the difficulty in finding an immunologically compatible donor [3,15,18,23,29,31]. Compared with non-sensitized patients, highly sensitized kidney transplant recipients often demonstrate worse clinical outcomes and lower graft and patient survival rates [4,10,13,16,20,26]. The formation of alloantibodies against human leukocyte antigens (HLA), which occurs as a result of blood transfusion, previous transplants, infections, or pregnancy, contributes to the development of sensitization. The proteolytic reactive antibody (PRA) test is widely used to assess the level of sensitization in potential kidney transplant

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recipients. Candidates with a PRA ≥80% are classified as highly sensitized [5,9,12,14,24,25,29] and those with a PRA ≥98% as extremely highly sensitized , giving them increased priority for organ allocation [6,12,19,21,27,32]. Desensitization is becoming an increasingly popular approach in transplantation for patients who would otherwise remain on dialysis without the possibility of receiving a transplant. Desensitization will also need to be considered in allocation policies as they are updated, as the number of patients who are immunized and highly immunized is increasing in most countries . Effective management of desensitization with an "acceptable" safety profile will require drug cocktails. Although approximately 30% of kidney transplant candidates on the waiting list are sensitized, only 6.5% receive a transplant each year [7,11,20,24,28,29,31]. In Europe, approximately 20% of patients waiting for a kidney transplant are sensitized, with 5% being highly sensitized [8,9,15,18,26,30].

Objective:

To improve the treatment outcomes of kidney transplantation in highly sensitized recipients through a comprehensive analysis of laboratory and morphological data of the transplant.

Materials and methods.

The duration of ESRD varied from **1 year to more than 10 years** . In most patients (85.2%), the disease lasted more than **4 years** , indicating the chronic nature of renal pathology and accumulation of sensitization. Statistical analysis showed that the average duration of the disease was **7.8 ± 3.2 years** . Long-term ESRD contributes to the development of chronic changes in the kidneys and increases the risk of immune complications after transplantation (Abecassis et al ., 2018).

The average age of patients was **32.0 ± 5.6 years.** (range 18-45 years) . The gender distribution was as follows: **18 men (66.7%)** And **9 women (33.3%) ,** which corresponds to a ratio of 2:1. This distribution is consistent with data from other studies, which also note a predominance of men among patients with end-stage renal disease (ESRD) (Kasiske et al ., 2018).

In the vast majority of patients, the cause of end-stage renal failure (ESRD) was chronic glomerulonephritis — **26 patients (96.3%) .** In one patient (**3.7%**), the cause of ESRD was interstitial nephritis. This distribution corresponds to data from national registries, where chronic glomerulonephritis is one of the leading causes of ESRD (United States Renal Data System [USRDS], 2020, Nephrology Registry of the Russian Federation, 2019).

All patients were screened for pre-existing antibodies using panel reactive antibodies (PRA) and donor-specific antibodies (DSA). PRA levels ranged from 25% to over 80% and DSA levels ranged from 500 to 5000 MFI (Mean Fluorescence Intensity).

Based on PRA and DSA values, patients were divided into two subgroups:

2A. Moderate sensitization : 17 patients (63.0 %) with PRA from 25% to 40% and DSA from 500 to 3000 MFI.

2B. High degree of sensitization : 10 patients (37.0 %) with PRA more than 40% and DSA more than 3000 MFI.

Statistical analysis showed that the average PRA level in the moderate sensitization group was **32.4 ± 4.5%** , and in the high sensitization group it was **65.7 ± 8.9%** . The differences were statistically significant (**p < 0.001**), which justifies dividing patients into subgroups for individualization of therapy.

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Analysis of mean PRA and DSA levels in sensitization subgroups showed that patients with a high degree of sensitization had significantly higher PRA and DSA levels compared with patients with a moderate degree of sensitization ($p < 0.001$). This statistically significant difference indicates the need for more intensive preoperative preparation in patients with high sensitization to reduce the risk of graft rejection. Our data are consistent with the results of studies by other authors indicating the importance of taking into account the degree of sensitization when planning therapy (Jordan et al ., 2017).

Table 1. Comparison of preoperative therapy regimens depending on the degree of sensitization

Component of therapy	Average sensitization	High sensitization
IVIg	1 g/kg	2 g/kg
Rituximab	No	375 mg/m² single dose
Plasmapheresis	2-3 sessions	3-5 sessions
Albumen	20 g after plasmapheresis	20 g after plasmapheresis
Tacrolimus	0.05 mg/kg/ day	0.05 mg/kg/ day
Mycophenolate mofetil	1 g/ day	1 g/ day
Induction therapy (ATG)	1.5 mg/kg/ day , 3 days	1.5 mg/kg/ day , 5 days

Patients with a high degree of sensitization received more intensive and prolonged therapy, including the use of rituximab and more plasmapheresis sessions. This approach is aimed at more effectively reducing antibody levels before transplantation, which is supported by data from studies [Vo et al ., 2014; Jordan et al ., 2017]. The use of rituximab in combination with IVIg and plasmapheresis showed high efficiency in desensitization of patients with high levels of PRA and DSA.

After preoperative therapy, a significant decrease in PRA and DSA levels was observed in all patients (Figure 1).

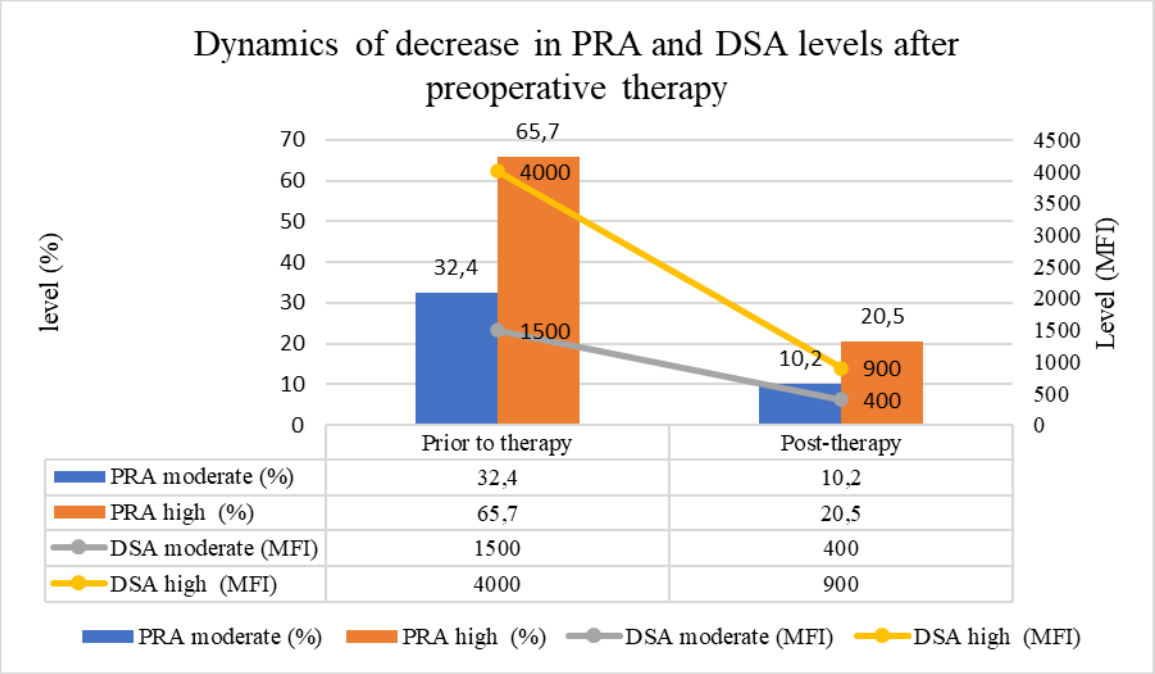

Figure 1. Dynamics of decrease in PRA and DSA levels after preoperative therapy

After preoperative therapy, statistically significant decreases in PRA and DSA levels ($p < 0.001$) were observed in patients of both groups. This indicates the effectiveness of the selected treatment regimens in reducing the degree of sensitization, which allowed kidney transplantation to be performed with a minimal risk of acute cellular or humoral rejection (see Figure 1).

46 ultrasound-guided puncture biopsies of transplants were performed at various times after surgery (see Table 2).

Table 2. Distribution of recipients by time of needle biopsy

Timing of needle biopsy	In the first hours after surgery	3rd day of p/t	7th day of work	9 days p/t	After 1 month p/t	After 6 months p/t
Number of patients	27 (58.7%)	10 (21.7%)	5 (11.0%)	2 (4.3%)	2 (4.3%)	0 (0%)
Total number of needle biopsies	46 (100%)					

First hours : biopsy was performed in all patients to assess the initial condition of the graft.

Repeat biopsies were performed when rejection or other complications were suspected, which allowed for timely adjustment of therapy.

Morphological assessment was performed according to Banff criteria, including indicators of interstitial inflammation (i), tubulitis (t) and intimal arteritis (v). The assessment results are presented in Table 3.

Table 3. Morphological changes according to Banff criteria

Criteria Banff classifications	i0	i 1	i 2	t0	t1	t2	v0	v1	v2
First day of work	27(58.7 %)	0	0	27(58.7 %)	0	0	27(58.7 %)	0	0
3-day p/t	7(15.2%)	1(2.2 %)	1(2.2 %)	5(10.9%)	2(4.3%)	1(2.2 %)	7(15.2%)	2(4.3%)	1(2.2 %)
7-day p/t	3(6.5 %)	1(2.2 %)	1(2.2 %)	4(8.7%)	1(2.2 %)	1(2.2 %)	3(6.5 %)	0	1(2.2%)
9-day p/t	1(2.2%)	1(2.2%)	1(2.2 %)	2(4.3%)	0	1(2.2 %)	1(2.2%)	1(2.2%)	1(2.2%)
In a month p/t	2(4.3%)	0	0	2(4.3%)	0	0	1(2.2%)	1(2.2%)	0
Total number of biopsies	46 (100%)			46 (100%)			46 (100%)		

Note: i - interstitial inflammation; t - tubulitis; v - intimal arteritis.

Interstitial inflammation ($i \geq 1$) and tubulitis ($t \geq 1$) were detected in 13.0% of patients on days 3–7 after transplantation, which corresponds to a moderate frequency of acute cellular rejection according to the Banff criteria.

Intimal arteritis ($v \geq 1$) was detected in 8.7 % of patients, indicating the presence of inflammatory processes in the arterial walls, which can negatively affect the blood supply to the graft and its function.

In this group of patients, the loss of the transplant was observed in a single case, in 6 patients the biopsy was assessed as manifestations of T-cell acute rejection, timely use of hormonal,

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immunosuppressive, antihistamine and dialysis therapy, it was possible to preserve the transplant in 5 patients, only 1 patient lost the transplant. Restoration of transplant function occurred only by the end of the first month after surgery.

Based on the above data, morphological assessment of biopsies revealed changes of varying severity, in some cases reaching the values of "i2", "t2" and " v 2" in combination. Considering that the morphological picture of changes of varying severity of the tubulointerstitial, vascular type has the same manifestations as inflammatory infiltration of the interstitium, in the case of "i2" inflammation reached up to 50% of unchanged cortical parenchyma. In tubulitis "t2" - foci with 5-10 mononuclear cells in the cross section tubules (or per 10 tubular epithelial cells). " v 2" - indicated severe intimal arteritis with narrowing of the lumen area along by at least 25% in at least one cross-section of the artery. In all cases of adequate and timely use of complex treatment procedures, restoration of graft function was noted at the end of the first month of treatment .

In patients with morphological signs of rejection, a significant deterioration in transplant function was observed, which is confirmed by an increase in the levels of endogenous intoxication indicators of urea and creatinine. Increased levels of these indicators are one of the key markers of deterioration in kidney transplant function and indicate a violation of its filtration capacity.

The leukocyte intoxication index (LII) is an important marker of systemic intoxication and inflammatory processes in patients after kidney transplantation. To assess the dynamics of LII, patients were divided into two subgroups depending on the degree of fluctuations in intoxication indicators:

- **Subgroup A** : 17 patients (63.0%) with minor fluctuations in LII.
- **Subgroup B** : 10 patients (37.0%) with significant fluctuations in LII.

This division made it possible to evaluate the differences in the dynamics of intoxication processes between patients with different degrees of severity of inflammatory reactions after transplantation (see Tables 4 and 5).

Table 4. Dynamics of LII in patients of subgroup A (n = 17)

The day after the operation	LII (mean ± SD)	p-value
Before surgery	1.5 ± 0.1	—
1 day	2.0 ± 0.2	$p < 0.05$ vs. before experiment.
3 days	1.7 ± 0.15	$p < 0.05$ vs. 1 day .
7 days	1.3 ± 0.1	$p < 0.01$ vs. 3 days .
Day 9	1.2 ± 0.1	$p > 0.05$ vs. 7 days .

Table 5. Dynamics of LII in patients of subgroup B (n = 10)

The day after the operation	LII (mean ± SD)	p-value
Before surgery	1.3 ± 0.1	—
1 day	2.1 ± 0.2	$p < 0.05$ vs. before experiment.
3 days	2.7 ± 0.25	$p < 0.01$ vs. 1 day .
Day 7	1.9 ± 0.15	$p < 0.05$ vs. 3 days .
Day 9	1.3 ± 0.1	$p < 0.01$ vs. 7 days .

Note: *p-values are calculated by comparison with the previous measurement.*

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Analysis of the dynamics of LII showed that in **subgroup A,** patients demonstrated **a moderate increase** in LII on **the 1st day** after transplantation (**2.0 ± 0.2** , $p < 0.05$) with a subsequent **decrease** to **1.2 ± 0.1** by **the 9th day** . While in patients of **subgroup B, a significant and prolonged increase in LII** was observed , reaching a peak on **the 3rd day** (**2.7 ± 0.25** , $p < 0.01$), which correlated with increased levels of body temperature, leukocytes and ESR. These results indicate **active inflammatory processes** And signs **transplant rejection** in patients of subgroup B requiring **enhanced immunosuppressive therapy .**

In addition to LII, patients with signs of rejection also had increased body temperature, white blood cell count, and erythrocyte sedimentation rate (ESR), which also reflects systemic inflammation and the immune response to the transplant (see Table 6).

Table 6. Dynamics of intoxication indices in patients of subgroup B (n = 10)

Indicator	Norm	Before surgery	1 day p/o	3 days p/o	7 days p/o	9 days p/o
Body temperature, °C	36.6	36.7 ± 0.04	37.8 ± 0.03***	38.1 ± 0.04***	37.2 ± 0.03***	36.5 ± 0.03***
Leukocytes, ×10⁹/l	6.0	7.2 ± 0.15	14.8 ± 0.12***	19.1 ± 0.10***	12.5 ± 0.08***	7.5 ± 0.08***
ESR, mm/h	10–15	17.0 ± 0.93	21.8 ± 0.66***	25.4 ± 0.47***	19.3 ± 0.34***	16.1 ± 0.16***

*Note: *** - statistically significant changes relative to the previous measurement ($p < 0.001$).*

In patients of subgroup B, a significant increase in body temperature, leukocyte level, and ESR was observed on the 1st and 3rd days after surgery, reaching a maximum on the 3rd day. Body temperature increased to 38.1 ± 0.04 °C , leukocyte level to 19.1 ± 0.10 × 10⁹/l , and ESR to 25.4 ± 0.47 mm/h . These indicators correlated with morphological signs of transplant rejection and required immediate correction of therapy. By the 9th day after transplantation, all indicators decreased, but they remained above normal, indicating a persistent inflammatory process.

The increase in LII and other intoxication indices in patients of subgroup B correlated with morphological signs of transplant rejection revealed during biopsy.

Statistically significant differences in the levels of LII, leukocytes and body temperature between subgroups A and B indicate that these parameters can be used as **markers for early detection of rejection .**

Timely correction of immunosuppressive therapy based on laboratory data improved treatment outcomes in patients with signs of rejection.

Of the total number of patients with signs of rejection **,** 6 **patients (18.5% of the total group)** managed to stabilize the graft function by the end of the first month after surgery. **1 patient (3.7%)** lost the graft despite the intensive therapy applied (Figure 2) , which coincides with the research data of Charat Thongprayoon (2023), approximately 30% of kidney transplant candidates on the waiting list are hypersensitive, and only 6.5% receive a transplant annually [7]. In Europe, approximately 20% of patients waiting for a kidney transplant are hypersensitive, with 5% of them being highly sensitive [8]. The incidence of acute rejection is 5.4%-9.2%. In our case, this figure was 3.7%, which confirms the effectiveness of the complex treatment procedure.

In 96.3% of cases, enhanced immunosuppressive therapy allowed stabilization of transplant function, which indicates the high effectiveness of the treatment approaches used.

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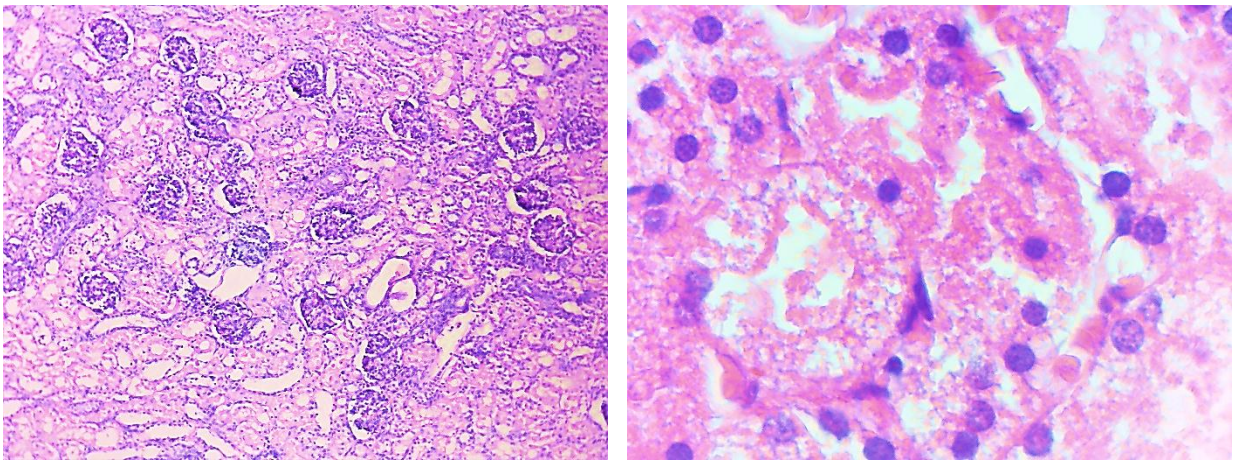
One patient lost the graft despite intensive therapy. This may be due to a high degree of sensitization, resistance to therapeutic interventions, or other concomitant factors.

Enhanced immunosuppressive therapy, including increased corticosteroid doses, ATG, and additional plasmapheresis sessions, is an effective method for stabilizing transplant function in patients with morphological signs of rejection. The high degree of statistical significance of differences in creatinine levels between groups confirms the effectiveness of the therapeutic approaches used. However, despite the high efficiency, there remains a small risk of transplant loss, which requires further research and optimization of treatment strategies.



A . **(i2)** CM G-E. 10x2. B. **(t2)** CM. G-E. 10x 4 .

Figure 2. Histological image of the graft showing signs of tubulitis (t2) and interstitial inflammation (i2).

Morphological examination of transplants is a key component of monitoring the condition of patients after kidney transplantation. Early detection of signs of rejection and timely correction of therapy allow preserving the function of the transplant and improving long-term outcomes.

Monitoring laboratory parameters of intoxication, including LII, leukocyte level, ESR and body temperature, is important for **early detection of transplant rejection** and timely correction of therapy. Patients with more pronounced and prolonged deviations of these parameters require special attention and **intensive immunosuppressive therapy .**

Conclusions

This article presents the results of a comprehensive examination and treatment of 27 recipients with a high degree of sensitization to a donor kidney transplant.

Morphological changes in the transplant, assessed by the Banff criteria, correlated with clinical and laboratory parameters, which emphasizes the importance of comprehensive monitoring of patients in the post-transplant period. Timely detection of signs of rejection and correction of immunosuppressive therapy allowed us to prevent transplant loss in most patients with morphological changes . In the world literature, the transplant rejection rate averages 7.3%, which we managed to reduce to 3.7%, which proves the effectiveness of the therapy.

Laboratory indicators of intoxication and inflammation, such as LII, leukocyte level, ESR and body temperature, serve as important markers of the patient's condition and require regular

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monitoring. Their dynamics allow us to evaluate the effectiveness of the therapy and promptly identify deviations.

Individualized therapy based on the degree of sensitization and response to treatment improves transplant outcomes and preserves graft function. This confirms the need for personalized treatment regimens and careful monitoring of highly sensitized patients.

Thus, the results of the study of this group of patients showed that kidney transplantation in patients with high sensitization expands the possibilities, since the tactics of patient management in the pre- and postoperative period developed by the dissertation candidate sharply reduces the sensitization of this category of patients and thereby contributes to a sharp reduction in the number of patients with high sensitization on the "waiting list", and accordingly to an increase in the frequency of transplant survival and an improvement in the percentage of postoperative complications. In addition, careful monitoring of laboratory parameters, such as LII, will provide specialists with early diagnosis of signs of rejection, which can be confirmed by morphological studies.

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